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Effect of immunosuppression maintenance in solid organ transplant recipients with COVID-19: Systematic review and meta-analysis

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Abstract

Background: The aim of this study was to assess the effect of continuing immune suppressive therapy in solid organ transplant recipients (SOTR) with coronavirus disease 2019 (COVID-19).

Methods: Systematic review and meta-analysis of data on 202 SOTR with COVID-19, published as case reports or case series. We extracted clinical, hemato-chemical, imaging, treatment, and outcome data.

Results: Most patients were kidney recipients (61.9%), males (68.8%), with median age of 57 years. The majority was on tacrolimus (73.5%) and mycophenolate (65.8%). Mortality was 18.8%, but an equal proportion was still hospitalized at last follow up. Immune suppressive therapy was withheld in 77.2% of patients, either partially or completely. Tacrolimus was continued in 50%. One third of survivors that continued immunosuppressants were on dual therapy plus steroids. None of those who continued immunosuppressants developed critical COVID-19 disease. Age (OR 1.07, 95% CI 1-1.11, $P = .001$) and lopinavir/ritonavir use (OR 3.3, 95%CI 1.2-8.5, $P = .013$) were independent predictors of mortality while immunosuppression maintenance (OR 0.067, 95% CI 0.008-0.558, $P = .012$) and tacrolimus continuation (OR 0.3, 95% CI 0.1-0.7, $P = .013$) were independent predictors of survival.

Conclusions: Our data suggest that maintaining immune suppression might be safe in SOTR with moderate and severe COVID-19. Specifically, receiving tacrolimus could be beneficial for COVID-19 SOTR. Because of the quality of the available evidence, no definitive guidance on how to manage SOTR with COVID-19 can be derived from our data.

KEYWORDS

COVID-19, immune suppression, outcome, solid organ transplant recipient, tacrolimus

Abbreviations: ACE2, angiotensin converting enzyme 2; ALT, alanine transaminase; ARDS, acute respiratory distress syndrome; AST, aspartate transaminase; CI, confidence interval; CNI, calcineurin inhibitors; COVID-19, Coronavirus Disease 2019; CRP, C-reactive protein; CT, computed tomography; F, female; ICU, intensive care unit; IL2r, interleukin-2 receptor; IL6, interleukin-2; IL7, interleukin-7; IQR, interquartile range; LDH, lactate dehydrogenase; M, male; mTOR, mammalian target of rapamycin; NIV, non invasive ventilation; OR, odds ratio; PRISMA, preferred reporting items for systematic reviews and meta-analyses; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SOTR, solid organ transplant recipient; SPSS, statistical package for social sciences.

1 | INTRODUCTION

The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in China in 2019 and rapidly spread worldwide[1] causing the new disease named Coronavirus Disease 2019 (COVID-19).[2]

Mechanisms of pathogenicity of SARS-CoV-2 have yet to be fully understood. In a review by Saddiqi and Mehra,[3] a three stage classification of COVID-19 clinical course, regardless of the baseline immune state, has been proposed. Stage 1 spans from inoculation to initial clinical symptoms. Following viral attachment to the ACE2 receptors, located in the lung, small intestine epithelium, and vascular endothelium, primary manifestations are respiratory, gastrointestinal and systemic.[4,5] During this phase, lymphopenia may ensue. Stage 2 is characterized by pulmonary involvement because of both direct viral effects and virus-triggered inflammation. Laboratory exams usually reveal lymphopenia, altered hepatic function, and lung computed tomography shows lung infiltrates. Hypoxia may already be present. Stage 3 is characterized by the rapid establishment of an excessive immune response generating a systemic hyper-inflammation syndrome, with major increase of inflammatory cytokines and biomarkers such as C-reactive protein (CRP), IL6, IL2r, IL7, ferritin, and D-dimer.[6] High levels of inflammatory cytokines and biomarkers correlate with a higher score of lung involvement on CT scan. Lung CT scan score can be used to identify severe cases, and the inflammatory storm and hypercoagulability can indicate a higher risk of progressing to multiorgan failure and death.[7]

Being a viral illness, COVID-19 could have a more complicated course in immunosuppressed hosts. However, the important role of the immune response in the late stages of the disease raises the question as to whether immune suppression could actually be protective in terms of disease progression. On the other hand, immune suppression could hamper or delay viral control generating a more prolonged immune stimulation, translating into a more severe clinical course and a higher chance of a negative outcome.

At present, COVID-19 clinical course and outcome in immune compromised patients, including solid organ transplant recipients (SOTR), seems to be grim, with mortality ranging between 20% and 30%.[8-10] Interestingly, most data published so far show the majority of SOTR with COVID-19 have either partially or completely withdrawn immune suppressive therapy. In an attempt to improve our understanding of the effects of ongoing immune suppressive therapy in COVID-19 SOTR, we performed a systematic literature review. We aimed to describe in better detail the clinical features and the outcome of COVID-19 in SOTR, with a specific focus on the effects of immune suppression changes.

2 | METHODS

2.1 | Study identification

This study is an individual patient data meta-analysis of SOTR with COVID-19. Publications in any form, including conference presentations, journal articles and non-peer-reviewed advance access publications, reporting data on SOTR with COVID-19, from January 1, 2020 to July 12 2020 were searched through PubMed, OVID, and Google Scholar. The search terms included "COVID-19," "transplant," "solid organ recipient," "SARS-CoV-2 infection."

2.2 | Study selection

Articles were included in our analysis if they provided information about every patient ≥18 years old and not presented in a collective manner but as single patient data. Thus, case reports and case series, regardless of the number of patients described, which provided information about each included case, were used. Articles were scrutinized for data retrieval and corresponding authors were contacted in order to obtain missing information if a specific information was not included in their article.

All relevant publications were used, irrespective of origin and type of article. While we searched for studies regardless of their language, only studies reported in English were included.

2.3 | Study and data extraction

Two investigators selected articles, evaluated the quality of the studies selected and entered findings independently into a database using data provided in figures, tables, and text. In case of disagreement, each case was discussed and controversy resolved through debate and mutual consensus. We ensured no overlapping data were used by giving a unique ID to each case included in the dataset.

2.4 | Inclusion/exclusion criteria

All SOTR patients ≥18 years old with confirmed SARS-CoV-2 infection through nasopharyngeal/oropharyngeal swab.

Non solid organ transplant recipients and patients younger than 18 years were excluded.

2.5 | Variables analyzed

For each patient, we extracted general clinical data, hemato-chemical parameters, chest imaging results, treatments received and disease outcome. Among the clinical data we sought, there were: age, sex; organ transplanted; immune suppressive regimens used; symptoms at onset of COVID-19; timing of COVID-19 relative to transplant; interval from symptom onset to hospital admission; comorbidities. Hemato-chemical parameters considered were blood cell count and differential, lactate dehydrogenase, C-reactive protein, procalcitonin, creatinine, alanine/aspartate aminotransferases (ALT/AST), D-dimer, ferritin, interleukin-6, tacrolimus plasma levels.

Presence of chest CT abnormalities compatible with COVID-19 was noted. A detailed analysis of immune suppressing agents used at onset and their handling during the disease course was performed. We also extracted and analyzed data on antiviral and/or immune modulating agent administration. Clinical classification was based on the worst clinical stage the patient progressed to. Accordingly, cases were classified in mild, moderate, severe and critical disease according to WHO guidelines.[11] Mild disease was defined as symptomatic patients meeting the case definition for COVID-19 without evidence of viral pneumonia or hypoxia; moderate disease as pneumonia without respiratory failure; severe disease as severe pneumonia with respiratory failure and oxygen saturation <90%; and critical disease as acute respiratory distress syndrome (ARDS). Predefined outcome considered was patient death.

2.6 | Statistical analysis

Most analyses were performed on data obtained at the time of admission. Numerical variables were presented as median and interquartile range (IQR), while categorical variables as number and percentage. The statistical significance of differences was evaluated by chi-square or Fisher's exact test for categorical variables and by Mann-Whitney U test for numerical variables. Items associated to outcomes at univariate analysis (P <.05) were included in a multivariate logistic regression model to identify covariates independently associated with the outcome of interest. All analyses were carried out with the aid of SPSS 25 (IBM, Armonk, NY, USA) with the assumption of a P-value ≤.05 as indicative of statistical significance of the observed differences and using two-sided tests.

3 | RESULTS

The literature search identified 790 articles. After exclusion of articles not regarding COVID-19 in SOTR, or articles regarding opinions, different protocols, or concerns about COVID-19 in SOTR, we identified 88 unique papers regarding COVID-19 in SOTR, including case reports, single- or multi-center studies irrespective of whether presenting information in a collective or single patient manner. Subsequently, after a full text review, we included in our analysis a total of 201 SOTR with COVID-19 from 67 articles[10,12-75] that met the inclusion criteria plus 1 case, a kidney transplant recipient admitted to our hospital. All articles except one (which was a preprint) were journal articles. The flow diagram of the literature search with exclusion criteria is presented in Figure 1 according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

Clinical features of SOTR with COVID-19 are shown in Table 1. SOTR with COVID-19 were mostly males (139 of 202, 68.8%), median age of 57 years. Most were kidney transplant recipients (61.9%), with a prior history of hypertension. Patients had a long median transplant history, 77 months. In terms of symptoms, most patients had fever (79.7%) and 93% were hospitalized as inpatients. Despite of the short time between symptom onset and admission (median 4 days), most patients (85.7%) had an abnormal

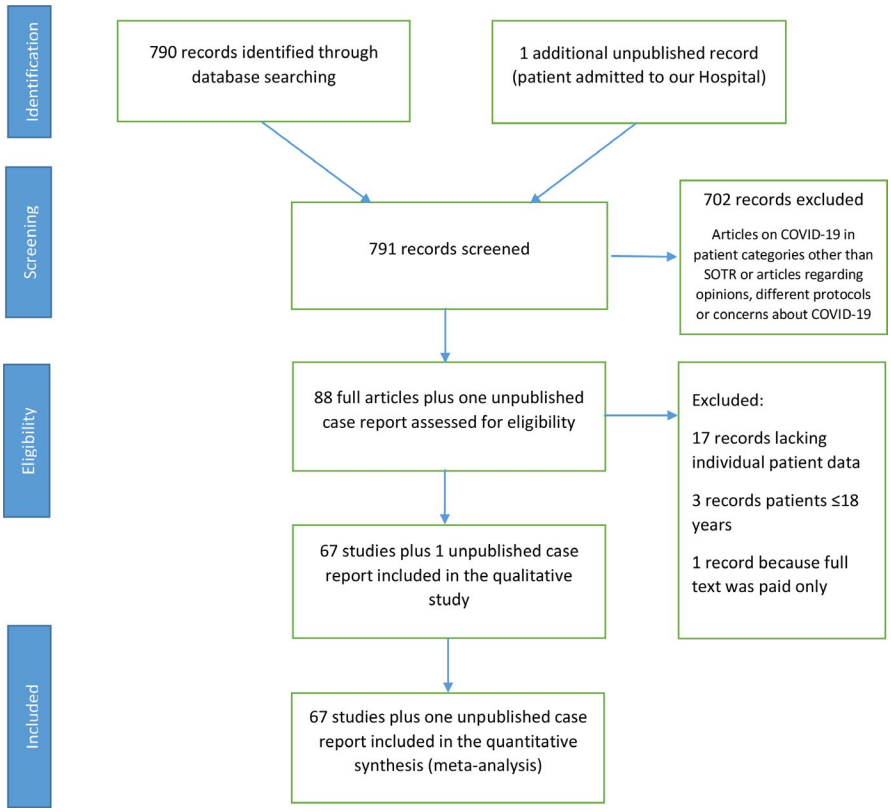

FIGURE 1 Flow diagram of the systematic literature regarding coronavirus disease 2019 in solid organ transplant recipient according to PRISMA statement

TABLE 1 Characteristics of 202 SOTR with COVID-19

Parameter	
Type of transplant	
Kidney	125 (61.9)
Liver	41 (20.3)
Kidney and liver	1 (0.5)
Kidney and pancreas	1 (0.5)
Heart	19 (9.4)
Heart and kidney	3 (1.5)
Lung	11 (5.4)
Face	1 (0.5)
Age	57 (49-67)
Sex	
M	139 (68.8)
F	63 (31.2)
Comorbidities (any)	160 (87.4)
Hypertension	120 (65.2)
Diabetes mellitus	16 (32.6)
Months after transplant	77 (24-173)
Immune suppressing agents	
Tacrolimus	147 (73.5)
Tacrolimus dose mg	4 [2-6.7]
Mycophenolate	131 (65.8)
Cyclosporin A	22 (10.9)
Steroids	139 (69.2)
mTor inhibitor	22 (10.9)
Azathioprine	13 (6.5)
Hematochemical data at baseline	
White blood cells, cells/μL	5460 [4000-7800]
Lymphocytes, cells/μL	651 [420-1107]
Lactate dehydrogenase, U/L	340 [271-511]
Procalcitonin, ng/mL	0.17 [0.08-0.3]
C-reactive protein, mg/L	50 [27-116]
Creatinine, mg/dl	1.7 [1.2-2.3]
Interleukin 6, pg/mL	58 [21-124]
D-dimer, ng/mL	1057 [641-2018]
Ferritine, ng/mL	593 [221-1156]
Tacrolimus blood levels, ng/mL	8 [6.6-16.05]
Symptoms at diagnosis	
Fever	161 (79.7)
Respiratory symptoms	144 (79.6)
Gastro-intestinal symptoms	61 (33.7)
Interval from symptom onset to diagnosis	4 days (1-7)
Abnormal lung CT scan at diagnosis	138 of 161 (85.7)
Medical treatment for COVID-19	
Antivirals	
Lopinavir regimen	49 (24.6)
Darunavir regimen	9 (4.5)
Hydroxychloroquine	128 (64.3)
Interferon	13 (6.5)
Remdesivir	6 (3)
Steroids	151 (74.8)
Intravenous immunoglobulin	25 (12.6)
Anti-Interleukin 6	37 (18.6)
Tacrolimus maintained	101 (50.8)
Mycophenolate maintained	34 (17)
Respiratory support	
Non-invasive ventilation	107 (59.1)
Invasive mechanical ventilation	48 (24.9)
Withdrawal of immune suppressors	
None	45 (22.8)
Partial or complete	152 (77.2)
Partial	86 (43.7)
Complete	66 (33.5)
COVID-19 disease	
Asymptomatic	2 (1.1)
Mild	15 (8.6)
Moderate	33 (18.9)
Severe	77 (44)
Critical	48 (27.4)
Outcomes	
Survived/Cured	124 (61.4)
Deceased	38 (18.8)
Ongoing hospitalization	38 (18.8)
Not specified	2 (1)

Note: Data are median (IQR) or number (%) if not otherwise specified.

finding on CT scan at hospitalization. On the other hand, 23 cases (11.3%) had a negative initial CT scan (Table 1). Most had normal white blood cell count on hospital admission (115 patients, median 5460, IQR 4000-7800 cells/mL), lymphopenia (108 patients, median 651, IQR 420-1107 cells/mL), elevated LDH (45 patients, median 340, IQR 271-511 U/L), high C-reactive protein (39 patients, median 50, IQR 27-116 mg/L), increased d-dimer (32 patients, median 1057, IQR 641-2018 ng/mL), high ferritin (31 patients, median 593, IQR 221-1156 ng/mL) and elevated IL-6 (21 patients, median 58, IQR 21-124 pg/mL). As most study patients were kidney transplant recipients, immune suppressors were modified in most cases (77.2%), either partially (43.7%) or completely withheld (33.5%). Tacrolimus was maintained in 50% of cases. Mycophenolate was maintained unchanged in 27 patients (13.5%) and reduced in 7 patients (3.5%). Most COVID-19 SOTR progressed toward respiratory failure (61.3%), which was treated with noninvasive ventilation in 59% and with invasive mechanical ventilation in 25% of cases.

The majority of patients were on a tacrolimus and mycophenolate regimen (Table 1). As intensity of immune suppression varies according to transplant age, we compared clinical features of SOTR according to transplant duration.

As shown in Table S1, COVID-19 outcome was not different in recipients grouped according to transplant duration, although differences were observed. Recently transplanted patients were younger (P =.023). The proportion of patients receiving tacrolimus (P < .001), and steroids (P =.032) was higher among those more recently transplanted and the opposite occurred for cyclosporin A (P =.001). There were no differences in terms of COVID-19 treatment between the two groups.

Definitive cure, defined as discharge to home after hospitalization and/or no need for further COVID-19 treatment for hospitalized or nonhospitalized patients, was reported in 61.4% of cases. Reported mortality was 18.8%, while 18.8% patients were still in hospital at the latest follow up and in 1% outcome was not specified. After excluding patients who were still hospitalized at the time of the report and those with unspecified outcome, we performed an analysis of factors associated with hospital mortality in 162 SOTR with COVID-19 (Table 2). An older age (P < .001), higher WBC, yet in the normal range (P =.035), higher LDH, IL-6, ferritin (P =.004, P =.002, P =.006) along with presence of respiratory symptoms (P =.016), presence of abnormal lung CT scan at hospitalization (P =.024), and treatment with lopinavir or darunavir regimens (P < .001, P =.038), invasive ventilation therapy (P =.000) were associated with a higher risk of mortality, while maintenance of previous immune suppression (P < .001) and ongoing treatment with tacrolimus (P < .001) were protective in terms of mortality. We then included in a multivariate analysis the four variables more strongly associated with mortality on the univariate analysis. Age (OR 1.07, 95% CI 1-1.11, P =.001) and treatment with a lopinavir-based regimen (OR 3.3, 95% CI 1.2-8.5, P =.013) were independent predictors of mortality while no change to the immune suppression therapy (OR 0.067, 95% CI 0.008-0.558, P =.012) and continuation of tacrolimus (OR 0.3, 95% CI 0.1-0.7, P =.013) were independent predictors of survival (Table 2).

Comparison of patients who did not change their immune suppression therapy with those that changed their therapy either partially or completely is presented in Table 3. The group that underwent changes to their immune suppression did not have more comorbidities but had a higher rate of hypertension (P =.001), a higher prevalence of mycophenolate (P =.001) and steroid treatment (P =.003), and had higher white blood cell count (P =.011), LDH (P =.028), and creatinine (P =.008). Also, these subjects had more often symptoms such as fever (P <.001) and pulmonary imaging positivity on diagnosis (P <.001), although lymphopenia was seen in both groups and respiratory symptoms, fever and abnormal pulmonary imaging were seen in more than 50% of cases continuing immune suppressive treatment. In the group that continued previous immune suppression, the worst COVID-19 disease stages observed were moderate and severe (33.3% and 35.8%). In contrast, most patients who underwent changes in their immune suppressive regimen progressed to severe and critical disease (45.4% and 35.6%) (P < .001 for comparison, Table 3).

In survivors who did not change regimen, 33.3% received dual therapy plus steroids, 12.8% dual therapy without steroids, 17.9% dual therapy including steroids and 35.8% received one drug (Table S2). Only 1 patient on dual therapy plus steroid died.

Sparse data were available regarding bacterial coinfection during hospitalization. Also, no information was found regarding thromboembolic complications.

Comparing patients that continued tacrolimus with those who withdrew it or did not receive any tacrolimus (Table 4), no differences were seen in terms of general comorbidities, although those who continued had more diabetes (P =.003), shorter transplant duration (P < .001), higher LDH (P =.015), lower CRP (P =.025), and lower creatinine (P =.022). They also had lower rates of fever and abnormal pulmonary imaging at diagnosis (P =.014, P =.019), although more than 70% of them were symptomatic and with positivity to imaging and 36% needed invasive ventilation. In the two groups, the worst COVID-19 disease was severe (42.3% no tacrolimus vs 46.5% tacrolimus), although critical patients were mostly observed in the tacrolimus withdrawal/no tacrolimus group (40% vs 14.7%).

In both groups the withdrawal of immune suppressive treatment and/or tacrolimus was associated with a greater use of steroids, lopinavir, and anti-interleukin-6 treatment.

Mycophenolate was continued in 34 patients (17%). Comparing patients that continued with those who withdrew or did not receive mycophenolate (Table 5), no differences were seen in terms of comorbidities and symptoms at diagnosis. However, patients treated with mycophenolate had lower LDH (P =.020), lower rates of hydroxychloroquine (P =.003), steroid (P =.016), and anti-IL-6 treatment (P =.050), and a better survival (P =.028). The rate of de novo steroid treatment was 7.8% in those who withdrew mycophenolate and 5.8% in those who did not (P = 1.000).

No differences in terms of outcome was seen between groups that continued only calcineurin inhibitors (CNI), only mycophenolate or both (Table S3).

4 | DISCUSSION

Our results suggest that COVID-19 in SOTR has a high mortality rate (18.8%). This figure might be underestimated, considering up to 18.8% of studied patients were still in hospital or on outpatient follow up without a definitive outcome. This mortality is higher than that seen in the overall population infected with COVID-19 (about 1.4%-7.2%),[76-79] compares to the mortality observed in COVID-19 ICU patients (25%)[80] and is in line with other studies on SOTR with COVID-19 (20%-30%).[8-10] However, information about median follow up time was not available in most cases, a limitation of our dataset.

In most initial studies on SOTR with COVID-19, immune suppressors were withheld partially or completely in most cases. Our

TABLE 2 Risk factors associated with hospital mortality in COVID-19 SOTR

	Outcome		Univariate analysis		Multivariate analysis	
Parameter	**Survived (N = 124)**	**Deceased (N = 38)**	**OR 95% CI**	***P* value**	**OR 95% CI**	***P* value**
Type of transplant						
Kidney	70 (56.4)	28 (60.5)		.910		
Liver	28 (22.5)	7 (18.4)				
Kidney and liver	1 (0.8)	0				
Kidney and pancreas	1 (0.8)	0				
Heart	14 (11.29)	2 (5.2)				
Heart and kidney	3 (2.4)	0				
Lung	7 (5.6)	1				
Age	54 [45-64]	63 [57-71]		**<.001**	1.07 (1.03-1.11)	.001
Sex						
M	88 (70.9)	23 (60.5)	0.6 (0.2-1.3)	.237		
F	36 (29)	15 (39)				
Comorbidities (any)	92 (82.8)	34 (94)	3.3 (0.7-15)	.160		
Hypertension	66 (59)	27 (75)	2 (0.8-4.7)	.113		
Diabetes mellitus	38 (34.2)	11 (30.5)	0.8 (0.3-1.9)	.839		
Months after transplant	73 [20-175]	102 [48-186]		.118		
Immune suppressing agents						
Tacrolimus	93 (75)	24 (64.8)	0.6 (0.28-1.3)	.293		
Tacrolimus dose mg	4 [2-7]	8.5 [5-]		.227		
Mycophenolate	80 (64.5)	26 (68.4)	1.3 (0.6-3)	.811		
Cyclosporin A	14 (11.2)	7 (18.4)	1.7 (0.6-4.7)	.274		
Steroids	81 (65.3)	26 (68.4)	1.15 (0.5-2.5)	.845		
mTor inhibitor	13 (10.4)	5 (13.1)	1.2 (0.4-3.8)	.768		
Azathioprine	8 (6.4)	3 (7.8)	1.2 (0.3-4.9)	.721		
Hematochemical data at baseline						
White blood cells, cells/μL	5040 [3900-6300]	7240 [4300-9100]		**.035**		
Lymphocyte, cells/μL	651 [423-1102]	715 [442-1175]		.618		
Lactate dehydrogenase, U/L	277 [246-372]	444 [317-737]		**.004**		
Procalcitonin, ng/mL	0.15 [0.07-0.28]	0.22 [0.12-0.3]		.296		
C-reactive protein mg/L	47 [19-88]	65 [34-172]		.069		
Creatinine, mg/dl	1.7 [1.13-2.2]	2.1 [1.4-3.4]		.157		

(Continues)

TABLE 2 (Continued)

Parameter	Outcome		Univariate analysis		Multivariate analysis	
	Survived (N = 124)	Deceased (N = 38)	OR 95% CI	*P* value	OR 95% CI	*P* value
Interleukin 6, pg/mL	24 [6.7-34]	141 [65-465]		**.002**		
D-dimer, ng/mL	961 [638-1470]	950 [540-2239]		1.000		
Ferritine, ng/mL	336 [157-875]	994 [817-2724]		**.006**		
Tacrolimus blood levels, ng/mL	7.7 [5.8-12.9]	8.5 [8.5-8.5]		.693		
Symptoms at diagnosis						
Fever	95 (76.6)	34 (89.4)	2.5 (0.8-7.9)	.108		
Respiratory symptoms	90 (75)	32 (90.9)	10.6 (1.3-81.4)	**.003**		
Gastro-intestinal symptoms	41 (34.1)	10 (26.3)	0.8 (0.3-1.9)	.835		
Interval from symptom onset to diagnosis	5 days [3-8]	4 [2-7]		.777		
Abnormal lung CT scan at diagnosis	91 (82.7)	26 (68)	0.7 (0.7-0.8)	**.024**		
Medical treatment for COVID-19						
Antivirals						
Lopinavir regimen	19 (15.3)	7 (18.9)	4.6 (2-10.4)	**<.001**	3.3 (1.2-8.5)	.013
Darunavir regimen	1 (0.8)	3 (8.1)	10.8 (1-107)	**.038**		
Hydroxychloroquine	75 (60.9)	27 (72.9)	1.7 (0.7-3.8)	.242		
Interferon	7 (5.6)	5 (13.5)	2.5 (0.7-8.7)	.150		
Remdesivir	3 (2.4)	1 (2.7)	1.1 (0.1-11)	1.000		
Steroids	88 (70.9)	28 (77.7)	1.4 (0.5-3.4)	.527		
Intravenous immunoglobulin	18 (12.2)	4 (10.8)	0.7 (0.2-2.2)	.786		
Anti-Interleukin 6	19 (15.4)	11 (29.7)	2.3 (0.9-5.4)	.058		
Tacrolimus maintained	75 (60.9)	10 (27)	0.2 (0.1-0.5)	**<.001**	0.3 (0.1-0.7)	.013
Mycophenolate maintained	28 (22.7)	3 (8.1)	0.2 (0.08-1)	**.058**		
Respiratory support						
Non-invasive ventilation	62 (53.9)	23 (74.1)	2.4 (1-5.9)	.064		
Invasive mechanical ventilation	11 (9.3)	24 (66.6)	19.4 (7.6-49.3)	**<.001**		
COVID-19 disease						
Asymptomatic	2 (2.1)	0		**<.001**		
Mild	13 (12)	0				
Moderate	30 (27.7)	0				
Severe	52 (48.1)	11 (31.4)				
Critical	11 (10.1)	24 (68)				

(Continues)

TABLE 2 (Continued)

Parameter	Outcome		Univariate analysis		Multivariate analysis	
	Survived (N = 124)	Deceased (N = 38)	OR 95% CI	*P* value	OR 95% CI	*P* value
Withdrawal of immune suppressors						
None	39 (32.2)	1 (2.7)	0.058 (0.008-0.442)	**<.001**	0.067 (0.008-0.558)	.012
Partial or complete	82 (67.7)	36 (97)				

Note: Data are median (IQR) or number (%).

P values denoting statistical significance of the differences are in bold.

data suggest that mortality was actually lower in SOTR who did not undergo changes to immune suppressive therapy. Up to 60% of patients who did not have their immune suppressive regimen changed were symptomatic and showed pulmonary imaging positive for COVID-19 pneumonia, suggesting that at baseline the disease could have progressed toward more severe stages also in these patients.

In a recent report, maintaining the immune suppressive therapy was recommended only for asymptomatic or milder cases, without high risk conditions (including comorbidities), and was not recommended in those receiving dual therapy plus steroids.[81] However, we observed that SOTR who continued their previous therapy developed as the worst presentation mostly moderate (33.3%) and severe (35.8) COVID-19, despite 80% of them had comorbidities and 33.3% were on dual therapy plus steroid. In contrast, those who modified immune suppressive regimen appeared to mostly progress toward severe (45%) and critical (35%) disease. There was an association between respiratory support requirement and reduction or discontinuation of immune suppression. In particular, patients in need for ventilatory support more frequently changed immunosuppression (Table 3). However, we are unable to define whether the oxygen requirement increased because of a change in immune suppression or rather the change in immune suppression was driven by a worsening respiratory condition. Mortality in the maintaining treatment group was 2.2% compared to 23.8% of those changing regimen. Thus, these data suggest that not only asymptomatic and mild cases could continue their previous immune suppressive regimen, but moderate and, possibly, severe cases as well.

Regarding critical patients, our data do not provide any answer. Interestingly, no patient who continued their immune suppressive treatment progressed to critical COVID-19. On the other hand, all patients who developed critical disease had their immune suppressive regimen changed/withdrawn. Thus, we believe that consideration should be given to the possibility that changes in immunosuppressive therapy may not correlate to a better outcome in SOTR with COVID-19. This hypothesis appears plausible in light of the studies suggesting that hyperinflammation and cytokine storm are related to mortality in COVID-19.[82,83]

A similar reasoning could apply to the use of tacrolimus, since the group that did not receive treatment with tacrolimus had higher baseline inflammatory markers and was significantly more symptomatic, showing more often a positive pulmonary imaging. However, in the group continuing tacrolimus, more than 70% were symptomatic and with positive lung imaging. More patients not treated with tacrolimus had a critical stage as their worst COVID-19 presentation (40% vs 14.7% in the tacrolimus group), although the two groups had a similar rate of severe COVID-19 (42.3% vs 46.5%). Interestingly, overall mortality was 27.3% vs only 9.9% among those maintaining tacrolimus.

Tacrolimus showed in vitro activity against SARS-CoV-1 and was therefore suggested as a potential COVID-19 treatment.[84,85]

Interestingly, mortality was already shown to be as low as 8% in a cohort of patients who continued their immune suppressive treatment with tacrolimus (96%), although at a reduced dose.[86]

TABLE 3 Characteristics of patients according to immune suppressive treatment suspension

	Withdrawal of immune suppressors		Univariate analysis	
Parameter	**None (N = 45)**	**Partially or complete (N = 152)**	**OR 95% CI**	***P* value**
Type of transplant				
Kidney	13 (28.8)	111 (73)		**<.001**
Liver	26 (57.7)	13 (8.5)		
Kidney and liver	1 (2.2)	0		
Kidney and pancreas	0	1 (0.6)		
Heart	2 (4.4)	17 (11.1)		
Heart and kidney	0	1 (0.6)		
Lung	3 (6.6)	6 (3.9)		
Face	0	1 (0.6)		
Age	54 [44-65]	58 [50-67]		.206
Sex				
M	30 (66.6)	105 (69)	1.1 (0.5-2.2)	.855
F	15 (33.3)	47 (30.9)		
Comorbidities (any)	34 (80.9)	122 (80.2%)	2 (0.7-5.2)	.177
Hypertension	18 (42.8)	100 (65.7)	3.6 (1.7-7.3)	**.001**
Diabetes mellitus	10 (23.8)	48 (31.5)	1.7 (0.7-3.8)	.192
Months after transplant	76 [13-202]	78 [30-165]		.870
Immune suppressing agents				
Tacrolimus	29 (64.4)	116 (76.3)	1.8 (0.8-3.7)	.121
Tacrolimus dose mg	2 [1-6]	4 [2-7]		.138
Mycophenolate	19 (42.2)	111 (73)	3.7 (1.8-7.5)	**<.001**
Cyclosporin A	6 (13.3)	20 (13)	0.9 (0.3-2.6)	1.000
Steroids	23 (51.1)	115 (75)	2.9 (1.4-5.9)	**.003**
mTor inhibitor	4 (8.8)	16 (10.5)	1.2 (0.3-3.8)	1.000
Azathioprine	5 (11.1)	8 (5.2)	0.4 (0.1-1.4)	.178
Hematochemical data at baseline				
White blood cells, cells/μL	4600 [3180-6217]	5600 [4500-8310]		**.011**
Lymphocyte, cells/μL	660 [350-1120]	640 [420-1105]		.946
Lactatate dehydrogenase, U/L	224 [151-292]	353 [272-545]		**.028**
Procalcitonin, ng/mL		0.17 [0.07-0.3]		–
C-reactive protein, mg/L	47 [10-98]	51 [31-126]		.366
Creatinine, mg/dl	1 [0.9-1.4]	1.9 [1.4-2.6]		**.008**
Interleukin, 6 pg/mL	26 [26-26]	62 [24-141]		.435
D-dimer, ng/mL	1020 [1020-1020]	1109 [609-2163]		.911
Ferritine, ng/mL		610 [266-1160]		**.006**
Tacrolimus blood levels, ng/mL	6.6 [3.2-7.2]	8.6 [7.6-21.7]		**.004**
Symptoms at diagnosis				
Fever	26 (59)	130 (85.5)	4.3 (2-9.1)	**<.001**
Respiratory symptoms	32 (72.7)	107 (81)	1.6 (0.7-3.5)	.286
Gastro-intestinal symptoms	9 (41)	50 (37.8)	0.4 (0.1-0.9)	**.042**
Interval from symptom onset to diagnosis	4 days [1-7]	4 [2-7]		.586
Abnormal lung CT scan at diagnosis	24 (61.5)	110 (93.2)	8.5 (3.2-22.5)	**<.001**

(Continues)

TABLE 3 (Continued)

Parameter	Withdrawal of immune suppressors		Univariate analysis	
	None (N = 45)	Partially or complete (N = 152)	OR 95% CI	*P* value
Medical treatment for COVID-19				
Antivirals				
Lopinavir regimen	3 (6.6)	44 (29.1)	5.7 (1.6-19.5)	**.001**
Darunavir regimen	0	9 (5.9)	1.3 (1.2-1.4)	.122
Hydroxychloroquine	16 (35.5)	109 (72.1)	4.7 (2.3-9.5)	**<.001**
Interferon	2 (4.4)	11 (7.2)	1.6 (0.3-7.8)	.736
Remdesivir	1 (2.2)	5 (3.3)	1.5 (0.1-13.2)	1.000
Steroids	21 (46.6)	129 (85.4)	6.7 (3.1-14)	**<.001**
Intravenous immunoglobulin	3 (6.6)	22 (14.6)	2.4 (0.6-8.4)	.207
Anti-Interleukin 6	3 (6.6)	34 (22.5)	4 (1.1-13.9)	**.017**
Tacrolimus continued	28 (63.6)	70 (46)	0.4 (0.2-0.9)	.059
Respiratory support				
Non-invasive ventilation	14 (31.8)	89 (66.9)	4 (2-8.9)	**<.001**
Invasive mechanical ventilation	0	47 (32.4)	1.4 (1.2-1.6)	**<.001**
COVID-19 disease				
Asymptomatic	2 (5.2)	0		**<.001**
Mild	10 (25.6)	5 (3.7)		
Moderate	13 (33.3)	20 (15.1)		
Severe	14 (35.8)	60 (45.4)		
Critical	0	47 (35.6)		
Outcomes				
Survived/cured	39 (86.6)	83 (54.9)		**<.001**
Deceased	1 (2.2)	36 (23.8)		
Ongoing hospitalization	5 (11.1)	33 (21.8)		

Note: Data are median (IQR) or number (%).

P values denoting statistical significance of the differences are in bold.

TABLE 4 Characteristics of patients according to ongoing treatment with tacrolimus

Parameter	Ongoing tacrolimus		Univariate analysis	
	No (N = 98)	Yes (N = 101)	OR 95% CI	*P* value
Type of transplant				
Kidney	72 (73.4)	51 (50.4)		**.010**
Liver	17 (17.4)	24 (23.7)		
Kidney and liver	0	1 (0.9)		
Kidney and pancreas	1 (1)	0		
Heart	7 (7.1)	12 (11.8)		
Heart and kidney	0	3 (2.9)		
Lung	1 (1)	9 (8.9)		
Face	0	1 (0.9)		
Age	58 [50-65]	56 [48-67]		.594
Sex				
M	71 (66.6)	67 (69)	1.3 (0.7-2.4)	.361
F	27 (33.3)	34 (30.9)		

(Continues)

TABLE 4 (Continued)

Parameter	Ongoing tacrolimus		Univariate analysis	
	No (N = 98)	Yes (N = 101)	OR 95% CI	*P* value
Comorbidities (any)	79 (88.7)	79 (86.8)	0.8 (0.3-2)	.821
Hypertension	63 (70)	57 (62.6)	0.7 (0.3-1.3)	.346
Diabetes mellitus	20 (22.2)	40 (43.9)	2.7 (1.4-5.2)	**.003**
Months after transplant	120 [54-193]	48 [13-97]		**<.001**
Hematochemical data at baseline				
White blood cells, cells/μL	5900 [4360-7947]	5040 [3547-7737]		.126
Lymphocyte, cells/μL	643 [420-1100]	680 [397-1132]		.738
Lactatate dehydrogenase, U/L	224 [151-292]	353 [272-545]		**.015**
Procalcitonin, ng/mL	0.18 [0.11-0.2]	0.16 [0.06-0.4]		.839
C-reactive protein, mg/L	67 [35-135]	40 [16-97]		**.025**
Creatinine, mg/dl	2.2 [1.7-2.8]	1.5 [1.1-1.9]		**.022**
Interleukin, 6 pg/mL	91 [21-229]	31 [20-63]		.192
D-dimer, ng/mL	707 [448-1290]	1194 [926-2692]		.052
Ferritine, ng/mL	830 [523-1754]	429 [157-1115]		.063
Symptoms at diagnosis				
Fever	85 (86.7)	73 (72.2)	0.3 (0.1-0.8)	**.014**
Respiratory symptoms	64 (82)	78 (77.2)	0.7 (0.3-1.5)	.462
Gastro-intestinal symptoms	32 (41)	28 (27)	0.5 (0.2-1)	.079
Interval from symptom onset to diagnosis	4 days [1-7]	4 [2-7]		.586
Abnormal lung CT scan at diagnosis	64 (94.1)	73 (80)	0.2 (0.08-0.7)	**.019**
Medical treatment for COVID-19				
Antivirals				
Lopinavir regimen	36 (37)	13 (12.8)	0.2 (0.1-0.5)	**<.001**
Darunavir regimen	9 (9)	0	0.4 (0.4-0.5)	**.001**
Hydroxychloroquine	66 (68)	62 (61.3)	0.7 (0.4-1.3)	.373
Interferon	8 (8.2)	5 (4.9)	0.5 (0.1-1.8)	.736
Remdesivir	1 (1)	5 (4.9)	5 (0.5-43)	.212
Steroids	81 (83.5)	69 (68.3)	0.4 (0.2-0.8)	**.014**
Intravenous immunoglobulin	16 (16.4)	9 (8.9)	0.5 (0.2-1.1)	.136
Anti-Interleukin 6	26 (26.8)	11 (10.8)	0.3 (0.1-1.6)	**.006**
Non-invasive ventilation	57 (64.7)	49 (53)	0.6 (0.3-1.1)	.171
Invasive ventilation	34 (36)	13 (13.4)	0.2 (0.1-0.5)	**<.001**
COVID-19 disease				
Asymptomatic	0	2 (2.3)		**<.001**
Mild	2 (2.3)	12 (13.6)		
Moderate	13 (15.2)	20 (22.7)		
Severe	36 (42.3)	41 (46.5)		
Critical	34 (40)	13 (14.7)		
Outcome				
Survived/Cured	48 (49.4)	75 (74.2)		**.001**
Deceased	27 (27.3)	10 (9.9)		
Ongoing hospitalization	22 (22.6)	16 (14.8)		

Note: Data are median (IQR) or number (%).

P values denoting statistical significance of the differences are in bold.

TABLE 5 Characteristics of patients according to ongoing treatment with mycophenolate

	Ongoing mycophenolate		Univariate analysis	
Parameter	No (N = 165)	Yes (N = 34)	OR 95% CI	*P* value
Type of transplant				
Kidney	107 (64.8)	17 (50)		.121
Liver	29 (17.5)	12 (35.2)		
Kidney and liver	1 (0.6)	0		
Kidney and pancreas	0	1 (2.9)		
Heart	16 (9.6)	3 (8.8)		
Heart and kidney	3 (1.8)	0		
Lung	8 (4)	1 (8.9)		
Face	1	0		
Age	57 [49-67]	57.5 [45-64]		.621
Sex				
M	114 (69.1)	23 (67.6)	1 (0.4-2.3)	.842
F	51 (30.9)	11 (32.3)		
Comorbidities (any)	128 (87)	30 (90.9)	1.4 (0.4-5.3)	.770
Hypertension	100 (67.5)	20 (60.6)	0.7 (0.3-1.6)	.542
Diabetes mellitus	48 (32.4)	12 (36.3)	1.1 (0.5-2.6)	.686
Months after transplant	83 [30-183]	76 [12-158]		.202
Hematochemical data at baseline				
White blood cells, cells/μL	5300 [3940-7800]	5900 [4300-7100]		.579
Lymphocyte, cells/μL	641 [420-1085]	700 [400-1500]		.861
Lactatate dehydrogenase, U/L	347 [272-531]	172 [154–]		**.020**
Procalcitonin, ng/mL	0.18 [0.1-0.31]	0.07 [0.07-0.07]		.329
C-reactive protein, mg/L	51.4 [31-119]	47 [18-97]		.525
Creatinine, mg/dl	1.9 [1.4-2.4]	0.9 [0.8-1.7]		**.003**
Interleukin, 6 pg/mL	62 [24-141]	26 [26-26]		.435
D-dimer, ng/mL	1022 [565-2410]	1133 [1020–]		.738
Ferritine, ng/mL	593 [251-1164]	915 [915-915]		.603
Symptoms at diagnosis				
Fever	135 (81.8)	23 (67.6)	0.4 (0.2-1.05)	.100
Respiratory symptoms	112 (77.2)	29 (85.2)	2.1 (0.7-6.5)	.236
Gastro-intestinal symptoms	51 (35.1)	9 (27.2)	0.6 (0.2-1.5)	.423
Interval from symptom onset to diagnosis	4 days [1-6]	7 [3-9]		**.021**
Abnormal lung CT scan at diagnosis	112 (86.8)	24 (80)	0.6 (0.2-1.7)	.571
Medical treatment for COVID-19				
Antivirals				
Lopinavir regimen	39 (23.7)	10 (29.4)	1.3 (0.5-3)	.515
Darunavir regimen	9 (5.4)	0	0.8 (0.7-0.8)	.362
Hydroxychloroquine	113 (68.9)	14 (41.1)	0.3 (0.1-0.6)	**.003**
Interferon	12 (7.3)	1 (2.9)	0.3 (0.04-3)	.702
Remdesivir	6 (3.6)	0	0.8 (0.7-0.8)	.592
Steroids	130 (78.7)	20 (58.8)	0.3 (0.1-0.8)	**.016**
Intravenous immunoglobulin	22 (13.3)	3 (8.8)	0.6 (0.1-2.2)	.580
Anti-Interleukin 6	35 (21.3)	2 (5.8)	0.2 (0.05-1)	**.050**

(Continues)

TABLE 5 (Continued)

Parameter	Ongoing mycophenolate		Univariate analysis	
	No (N = 165)	Yes (N = 34)	OR 95% CI	*P* value
Non-invasive ventilation	89 (60.9)	16 (48.4)	0.6 (0.2-1.2)	.240
Invasive ventilation	43 (27.2)	4 (12.1)	0.3 (0.1-1.1)	.077
COVID-19 disease				
Asymptomatic	2 (1.3)	0		.135
Mild	10 (6.9)	5 (17.2)		
Moderate	25 (17.3)	8 (27.5)		
Severe	64 (44.4)	12 (41.3)		
Critical	43 (29.8)	4 (13.7)		
Outcome				
Survived/Cured	95 (57.9)	28 (82.3)		**.028**
Deceased	34 (20.7)	3 (8.8)		
Ongoing hospitalization	35 (21.3)	3 (8.8)		

Note: Data are median (IQR) or number (%).

P values denoting statistical significance of the differences are in bold.

The protective role of immune suppression from CNI in transplanted patients or steroids in general population is being assessed. For instance, one study described protective effects of cyclosporine (CNI) treatment in transplanted patients.[87] An ongoing clinical trial is assessing treatment with tacrolimus and methylprednisolone for COVID-19 patients.[88] Discontinuation of immune suppressors did not provide any benefit to a cohort of liver transplant recipients.[89] A beneficial effect of steroids in lowering COVID-19 associated mortality has been suggested.[90,91] From our observation, steroid treatment was not related to survival. However, it was associated with immune suppressive treatment withdrawal and negatively correlated to tacrolimus and mycophenolate continuation.

Mycophenolate is the first immune suppressive drug to be withdrawn in kidney transplant patients <60 years old with pneumonia without hypoxemia and in patients >60 years old even without pneumonia.[92] Since its effect in inhibition of B lymphocytes,[93] the consideration is that mycophenolate could have a negative effect regarding COVID-19 in SOTR.[94] However, in a study by Cheng et al,[95] mycophenolate was shown to have antiviral activity against MERS-CoV by inhibiting Papain-like protease, a protein found to regulate viral spread for SARS-CoV-2 too.[96] Our data suggest that mycophenolate also exerted a protective effect in terms of COVID-19 mortality, although to a lower extent than tacrolimus.

Treatment with lopinavir was not associated with survival, in line with previous studies.[97,98] In SOTR, many patients withdrew tacrolimus to start lopinavir/ritonavir because of their pharmacokinetic interaction, making it particularly difficult to give both drugs concurrently.[99]

Our study has several limitations, mostly inherent to the type of analyzed data. For many patients follow up was not complete and many were still hospitalized at the time of reporting. However, we did not include this subset of patients in the analysis of outcome. We could not provide any data on mid-term follow up or other transplant related outcomes, including de novo donor specific antibody formation or subsequent graft loss. The beneficial effect of continuing immune suppression could have been the result of confounders that, based on available data, could not be accounted for in our analysis. Also, we acknowledge that the therapeutic approach used in included patients may be outdated because of fast changing knowledge on this new disease. Finally, we could not provide definitive data on the timing of immune modification in relation to the time course of infection.

In conclusion, our study suggests that ongoing immune suppressive therapy may be safe in moderate and severe COVID-19 SOTR, and that treatment with tacrolimus and, possibly, mycophenolate, may be associated with survival. Further studies are needed to corroborate our results and to provide further answers to the question of how to optimally manage immune suppression in SOTR with COVID-19. Because of the quality of the available evidence, we could not provide more definitive guidance on how to manage SOTR with COVID-19.

DISCLOSURE

The authors declare no conflicts of interest.

AUTHORS CONTRIBUTION

AK, RZ, EDM worked on concept of the study; SP, AS worked on data collection and data interpretation; FB, FP, MG worked on statistical analysis; AK, RZ and EDM drafted the manuscript; CM and all authors critically revised the manuscript.

DATA AVAILABILITY STATEMENT

The dataset generated for this study are available on request to the corresponding author.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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